Species Proposal For A Chronic Toxicity/Carcinogenicity Study with P-08-509

In repeated dose toxicity studies in rats and mice with P-08-509, the lowest observed effect levels in both species occur in the liver and are consistent with a peroxisome proliferator alpha ($PPAR_{\alpha}$) agonist. Changes in serum lipids and proteins, which are also common finding with $PPAR_{\alpha}$ agonist, are seen in both species as well. For the upcoming carcinogenicity study with P-08-509, we recommend the rat as the test species of choice for the reasons outlined below.

1. *Absence of unique toxicity in mice compared to rats*

   Although effects in mice are generally seen at lower external doses of P-08-509, most findings observed to date occurred in both species without any significant unique target organ toxicity in either species. Therefore, the studies conducted to date, which include exposures of up to 90 days in both species, do not predict any unique targets for carcinogenicity in the mouse compared to the rat.

2. *Responsiveness of the rat to liver effects*

   As noted above, most effects, including liver effects, occur at lower external doses of P-08-509 in mice compared to the rat. However the studies conducted to date clearly demonstrate that liver effects will occur in rats at (and likely below) a maximum tolerated dose of P-08-509. This includes trophic responses in the liver that could lead to proliferative lesions following chronic exposure to the compound. In addition, the general susceptibility of the rat liver to both neoplastic and nonneoplastic changes following exposure to peroxisome proliferators, including other perfluoro acids (PFA), is well established.

3. *Responsiveness of the rat to other tumor types*

   In addition to liver effects, peroxisome proliferators, including some PFAs, have been shown to produce benign tumors in the testes (interstitial cell tumors) and pancreas (acinar cell tumors) of rats. These tumor types have also been observed in rats following chronic exposure to other classes of drugs and chemicals. However, such tumors are relatively rare in mice both as spontaneous lesions and as xenobiotic-induced tumors. Although the human relevance of testicular interstitial cell tumors and pancreatic acinar cell tumors in rats is uncertain, detection of this response in a rodent carcinogenicity bioassay would require that the study be conducted in rats.

4. *Comparison of rat data to existing carcinogenicity data for other compounds*

   Most chronic toxicity/carcinogenicity data on peroxisome proliferators, and more

importantly, for other selected PFAs, has been generated in the rat. Thus, comparison of data from a carcinogenicity study with P-08-059 to existing rodent cancer data for other compounds will be greatly facilitated if the study is conducted in rats.

In summary, studies conducted to date with P-08-509 do not suggest any significant unique target organ toxicity, including liver toxicity, for this compound in the mouse compared to the rat. In contrast, existing carcinogenicity studies with similar compounds demonstrate the potential for induction of certain tumor types for which the rat, but not the mouse, appears to be susceptible. Finally, comparison to carcinogenicity data for existing compounds of similar mechanism of action and/or chemical class will be facilitated by use of the rat. Therefore, we consider the rat to be the species of choice for a chronic toxicity/carcinogenicity study with P-08-059.